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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,845	06/27/2001	Xavier Paliard	1681.002	3705

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CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/894,845	PALIARD	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,7,10-12,15-21 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,10-12,15-21 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 1/16/2007.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 1-3, 6, 7, 10-12, 15-21, 41 are examined herein.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 1/16/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3, 6, 7, 10-12, 15-19 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorczynski et al. (Cellular Immunology, 1995, cited by Applicants) in view of Nakai et al. (Blood, 1998; Vol. 91, pages 4600-4607), and further in view of Wakita et al. (JBC, 1998, cited by Applicant), for the reasons of record (e.g., see 10/18/2005 Office Action), which are reiterated herein for convenience.

Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorczynski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorczynski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal (e.g., see Nakai et al, 1998). Furthermore, the prior art also recognizes that a transgenic animal that expresses specific HCV genes in its liver can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection. (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice and as long as the transgene was present it would be expressed in the animal).

Nakai specifically teaches the sustained expression of a gene in the liver of an animal using an adeno-associated viral particle that expresses human blood coagulation factor IX (i.e., the immunogen) wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., see abstract; page 4601; page 4603, Figures 2 and 3, etc.).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a transgenic mouse results in an animal that can

be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to an HCV gene (i.e., HCV E1 or HCV E2) can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings based on the teaching of Wakita that an animal that expresses an HCV transgene in the liver of an animal results in an animal that is "a powerful tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract of Wakita). Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

Claims 1-3, 6, 7, 10-12, 15-21 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorczynski et al. (Cellular Immunology, 1995, cited by Applicants) in view of Nakai et al. (Blood, 1998; Vol. 91, pages 4600-4607), further in view of Wakita et al. (JBC, 1998, cited by Applicant) and further in view WO 97/47358 (Donnelly et al.), for the reasons of record (e.g., see 10/18/2005 Office Action) which are reiterated herein for convenience.

As indicated above, Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal.

Specifically, Gorczynski teaches a method of making a mouse (i.e., a rodent) that is tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse (e.g., see abstract; page 224; page 225, column 1, etc.).

However, Gorczynski does not teach that the immunogen is a protein that is encoded by a nucleic acid that is delivered by portal vein injection. However, the prior art teaches that portal vein delivery of an adeno-associated viral particle encoding a specific protein results in the sustained expression of encoded protein in the liver of the animal (e.g., see Nakai et al, 1998). Furthermore, the prior art also recognizes that a transgenic animal that expresses specific HCV genes in its liver can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection. (e.g., see Wakita et al. 1998, it is noted that the mice of Wakita are transgenic mice and as long as the transgene was present it would be expressed in the animal), and the HCV NS5a gene was recognized in the prior art as an HCV gene which could be used to raise an immunological response to HCV in an animal (e.g., see Donnelly et al.).

Nakai specifically teaches the sustained expression (8-10 months) of a gene in the liver of an animal using an adeno-associated viral particle that expresses human blood coagulation factor IX (i.e., the immunogen) wherein the adeno-associated viral particle is delivered to the liver by portal vein injection (e.g., see abstract; page 4601; page 4603, Figures 2 and 3, etc.).

Wakita specifically teaches that conditional transgene expression of nucleic acids encoding HCV E1 and HCV E2 in the liver of a transgenic mouse results in an animal that can

be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection.

Donnelly specifically teaches a nucleic acid encoding the HCV NS5a gene (e.g., see Figure 12) which can be used to raise an immunological response to HCV in animal (e.g., see page 1, lines 16-21; page 3, lines 17-31; page 10, line 31 through page 1 line 35; page 20, lines 14-17; claims 1, 2, 15; etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to the HCV NS5a gene can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings and make the HCV NS5a tolerant animal based on the teaching of Wakita that an animal that expresses an HCV transgene in the liver of an animal results in an animal that is "a powerful tool with which to investigate the immunoresponses and pathogenesis of HCV infection" (see abstract of Wakita), and also in view of the teaching of Donnelly that HCV NS5a is a specific immunogenic HCV gene. Furthermore, it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

Response to Arguments

Applicant's arguments on pages 5-13 of the communication filed 1/16/2007 have been fully considered, but are not persuasive.

In response to the rejection of claims 1-3, 6, 7, 10-12, 15-19 and 41 under 35 U.S.C. 103(a), Applicant argues that there are no suggestions in the cited references to arrive at the claimed invention. Applicants assert that previously described transgenic animal models do not provide good models of tolerance because transgenic animals, which express HCV antigens at birth, are inherently tolerant to those antigens. Applicants contend that the immune system views antigens present at birth as "self" antigens; therefore, animal models in which the antigens are expressed at birth, do not provide a model of tolerance to non-self antigens. Applicants assert that the instant application provides a non-germline animal model of tolerance that more accurately mimics the natural development of tolerance during chronic HCV infection, and refer to the specification at page 3, lines 10-29.

In response, it is noted that page 3, lines 24-29 specifically indicates:

> "Additionally, Wakita et al. (1998, J. Biol. Chem., 273:9001-6) developed a germline transgenic mouse, using the cre/lox system, for the **inducible** expression of HCV proteins (C, El, E2 and NS2) in the adult animal, to study the immune response to and pathogenesis of HCV infection. All **non-inducible** germline transgenic HCV models, however, would be expected to be inherently 'tolerant' to the particular HCV antigen expressed, as the mice express the proteins at birth and their immune systems see them as 'self.'" (Emphasis added).

Therefore, the specification acknowledges that it is **non-inducible** germline transgenic HCV models that would be expected to be inherently 'tolerant' to the particular HCV antigen expressed. The specification also acknowledges that the transgenic animal taught by Wakita has a system for **inducible** expression of HCV proteins, which would not be expected to be inherently tolerant to particular HCV protein expressed, as the HCV protein could be induced sometime well after birth such that their immune systems see not see them as "self."

With respect to the Gorczynski reference, Applicant argues that Gorczynski is directed to the injection of spleen cells, something very different and distinct from an antigen from an organism that causes an infectious disease, specifically an HCV immunogen as claimed. Applicant also argues that Gorczynski demonstrates tolerance to skin allografts but suggests nothing with respect to tolerance to an antigen from an organism that causes an infectious disease, specifically an HCV immunogen as claimed and that Gorczynski does not teach expression of an immunogen for at least one month. Applicant asserts that Gorczynski discloses a model for allograft tolerance, and does not give any direction or guidance on how to induce tolerance to any infectious agent.

With respect to the Nakai reference, Applicant argues that Nakai fails to cure the deficiencies of the Gorczynski because it does not disclose anything about HCV and fails to teach or suggest any method for inducing tolerance to an antigen in an animal model as claimed. Applicant argues that the human factor IX expressed is not in any way related to an antigen or immunogen from an infectious agent, specifically an HCV immunogen as claimed.

With respect to the Wakita reference, Applicant argues Wakita pertains to conditional expression of HCV proteins in transgenic mice in order to generate an antibody response and that antigens are produced only transiently, as opposed to sustained expression for at least one month as claimed. Applicants assert that Wakita teaches away from the claimed invention.

With respect to the Donnelly reference, Applicants argue that there is nothing in the Donnelly reference to cure the deficiencies of Gorczynski, Nakai, and Wakita. Applicants assert that Donnelly is silent on the expression of antigens to induce immunological tolerance to HCV antigens and is instead directed to expression of HCV antigens and contend that Donnelly fails to

teach or suggest anything regarding nucleic acid immunization by injection in the portal vein, or sustained expression of antigens in the liver to achieve immunological tolerance.

Applicant respectfully submit that the combined references do not encompass all of the claimed limitations, since none of the references teach or suggest sustained expression of an HCV immunogen for at least one month to induce tolerance to the immunogen. Applicant also argues that the Examiner has failed to identify the motivation for combining the references.

In the instant case, the claimed invention is obvious in view of the teachings of the cited references (Gorczynski, Nakai, Wakita and Donnelly) for the reasons of record, which are reiterated above. Specifically, the prior art teaches: (1) the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal (Gorczynski), (2) that a protein of interest can be expressed in the liver of an animal for more than a month using an adeno-associated viral particle encoding the protein of interest when the viral particle is delivered by portal vein delivery (Nakai; e.g., see Table 1, Figure 5, etc.), (3) a mouse that expresses HCV transgenes in its liver is a powerful tool for studying immune response and pathogenesis of HCV infection (Wakita), and (4) HCV NS5a gene is an HCV immunogen which can be used to raise an immunological response in animal (Donnelly). It would have been prima facie obvious to one of ordinary skill in the art of creating animal models for screening agents that modulate to a viral immunogen that the cited references could be combined to make the claimed invention with a reasonable expectation of success. Furthermore, one of ordinary skill in the art would understand that making such animal models would be desirable based on the teaching of Wakita

that a transgenic mouse that expresses HCV genes in the liver can be used an a model for to understand immunological phenomena in HCV infections (as indicated above).

It is acknowledged that Wakita only teaches transient expression of HCV transgenes. However, it is respectfully pointed out that Nakai teaches a method for sustained expression of a transgene in the liver of an animal for more than a month. It is also acknowledged that Wakita does not teach that the animal that transiently expresses the HCV transgene is a "tolerant" animal model. However, Wakita does explicitly teach that conditional transgene expression of HCV transgenes in the liver of a transgenic mouse results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection. Furthermore, Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal. Therefore, considering the teachings of the prior art as a whole, the prior art taught all of the limitations of the claims, there was sufficient motivation to one of ordinary skill in the art to combine the teachings and there was a reasonable expectation of success.

Applicant submits that the cited references do not disclose or suggest all the limitations of the present invention, because none of the references suggests sustained expression for at least one month of an antigen from an infectious agent, in particular an HCV immunogen and, as such, a prima facie case of obviousness has not been established. Applicant also asserts that the Examiner has not provided any evidence indicating a motivation which would have provided reasonable expectation of success in combining the references to arrive at the claimed invention.

In response, it is respectfully submitted that the cited references, as a whole, do teach all of the limitations of the claims. Specifically, Wakita teaches that an mouse that expresses HCV transgenes in its liver is a powerful tool for studying immune response and pathogenesis of HCV infection, Nakai teaches a method for long term expression of a transgene in the liver of a mouse and Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal and Donnelly teaches the HCV NS5a gene is an HCV immunogen which can raises an immunological response in animal.

Applicant (citing MPEP 2143.01) asserts that the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. Applicant contends that since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references.

In response, it is respectfully pointed out that MPEP 2143.01 indicates:

> "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.)...
> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to

> those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992)..."

In the instant case, the combined teachings, the knowledge of one of *ordinary* skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art that the cited references could be combined to make the claimed invention with a reasonable expectation of success. One of ordinary skill in the art would recognize the desirability for creating a mouse that expresses HCV transgenes in its liver for an extended period of time (i.e., more than a month) to create an animal model that is a powerful tool for investigating the immune responses and pathogenesis of HCV infection (as taught by Wakita) and/or to create an animal that is tolerant to the sustained presence of an immunogen in the liver of the animal (as taught by Gorczynski).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). In this case, the teaching of Gorczynski that the sustained presence of an immunogen in the liver of an animal can produce tolerance to the immunogen, provides motivation to express a protein in the liver of an animal in order to induce tolerance to the foreign protein. In view of the teachings of Nakai, one of ordinary skill in the art would have

the knowledge to recognize that portal injection of a vector that expresses a protein is a convenient way of producing an animal that has sustained expression a foreign gene in the liver of an animal, thus providing motivation to combine the references. Also, the teachings of Wakita that an animal that expresses an HCV transgene in its liver is an animal that is "a powerful tool with which to investigate the immunoresponses and pathogenesis of HCV infection" provides the motivation for combining the references in order to make an animal model that is tolerant to an HCV transgene, and Donnelly teaches that the HCV NS5a gene is an HCV immunogen. Therefore, the HCV NS5a gene is a specific HCV gene that could be used in the claimed method.

Therefore, considering the teachings of the prior art, as a whole, the claimed method is prima facie obvious. Specifically, considering that (1) Gorczynski teaches the general concept that animals that are immunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of the animal, (2) Nakai teaches a method for long term expression of a transgene in the liver of a mouse (8-10 months), (3) Wakita teaches that an mouse that expresses HCV transgenes in its liver is a powerful tool for studying immune response and pathogenesis of HCV infection, and (4) Donnelly teaches that the HCV NS5a gene is an HCV immunogen which can be used to raise an immunological response in animal, it would have been prima facie obvious to one of ordinary skill in the art, at the time of filing, to combine the cited references in order to make the claimed invention. Furthermore, considering the teaching of Gorczynski that sustained presence of an immunogen in the liver induces tolerance, there would have been a reasonable expectation that combining the cited references would be successful in inducing tolerance to an HCV transgene such as HCV NS5a.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on 9:00 a.m.- 6:00 p.m., Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JON E. ANGELL, PH.D.
PRIMARY EXAMINER